

subsequent product serials, as described in paragraph (c) below. The reference shall be qualified as follows:

(1) At least 20 newborn, colostrum-deprived animals of the species for which the product is recommended shall be randomly selected.

(2) Blood samples shall be taken from each animal.

(3) Each animal shall be administered one dose of reference by the recommended route and shall be observed for 24 hours.

(i) Any adverse reactions shall be recorded.

(ii) The dosage of reference administered to each animal shall be in accordance with label directions. Label directions may indicate a single dosage regardless of weight, in which case the animals in the study shall be at or near the maximum weight for neonates of the species.

(4) After 24 hours, blood samples shall be taken from each animal.

(5) Pretreatment and post treatment serum IgG concentrations shall be concurrently determined for each animal using a radial immunodiffusion (RID) method acceptable to APHIS and described in the filed Outline of Production for the product.

(6) Concurrently, using the same method, five IgG measurements shall be made on an IgG Species Standard supplied or approved by APHIS. The IgG Species Standard shall be a preparation that contains IgG specific for the species in question at a concentration acceptable to APHIS.

(7) For an IgG Reference Product to be satisfactory, all animals used to qualify the reference must remain free of unfavorable product-related reactions and at least 90 percent of the paired serum samples must reflect an increase in IgG concentration (posttreatment minus pretreatment concentration) equal to or greater than the IgG concentration of the IgG Species Standard.

(b) *Antibody functionality.* Prior to licensure, the prospective licensee shall perform a neutralization study, or another type of study acceptable to APHIS, to demonstrate functionality of product antibody.

(c) *Potency.* Bulk or final container samples of completed product from

each serial shall be tested for IgG content as provided in this paragraph. Samples of the test serial and of an IgG Reference Product established in accordance with paragraph (a) of this section shall be concurrently tested for IgG content by the RID method referred to in paragraph (a)(5) of this section. Five IgG measurements shall be made on each. If the IgG level per dose of the test serial does not meet or exceed that of the reference, one complete retest, involving five IgG measurements on both the reference and two samples of the test serial, may be conducted. If, upon retest, the average IgG level per dose of the two samples of the test serial does not meet or exceed that of the reference, or if a retest is not conducted, the serial is unsatisfactory.

[61 FR 51777, Oct. 4, 1996]

## PART 114—PRODUCTION REQUIREMENTS FOR BIOLOGICAL PRODUCTS

### Sec.

- 114.1 Applicability.
- 114.2 Products not prepared under license.
- 114.3 Separation of establishments.
- 114.4 Identification of biological products.
- 114.5 Micro-organisms used as seed.
- 114.6 Mixing biological products.
- 114.7 Personnel at licensed establishments.
- 114.8 Outline of Production required.
- 114.9 Outline of Production guidelines.
- 114.10 Antibiotics as preservatives.
- 114.11 Storage and handling.
- 114.12 Expiration date required.
- 114.13 Expiration date determination.
- 114.14 Extension of expiration date for a serial or subserial.
- 114.15 Disposal of unsatisfactory products and byproducts.
- 114.16 Producing subsidiaries.
- 114.17 Rebottling of biological products.
- 114.18 Reprocessing of biological products.

AUTHORITY: 21 U.S.C. 151–159; 7 CFR 2.22, 2.80, and 371.4.

SOURCE: 39 FR 16869, May 10, 1974, unless otherwise noted.

### § 114.1 Applicability.

Unless exempted by regulation or otherwise authorized by the Administrator, all biological products prepared, sold, bartered or exchanged, shipped or delivered for shipment in or from the

United States, the District of Columbia, any Territory of the United States, or any place under the jurisdiction of the United States shall be prepared in accordance with the regulations in this part. The licensee or permittee shall adopt and enforce all necessary measures and shall comply with all directions the Administrator prescribes for carrying out such regulations.

[52 FR 11026, Apr. 7, 1987, as amended at 56 FR 66784, Dec. 26, 1991]

**§ 114.2 Products not prepared under license.**

(a) When an establishment license is issued, if biological products which were not prepared in compliance with the regulations are in the establishment, such products shall not be shipped or delivered for shipment or otherwise dealt with as having been prepared under such regulations.

(b) Except as provided in 9 CFR part 103, a biological product shall not be prepared in a licensed establishment unless the person to whom the establishment license is issued holds an unexpired, unsuspended, and unrevoked product license issued by the Administrator to prepare such biological product, or unless the products prepared are subject to the provisions of § 107.2 of this subchapter.

(c) A biological product produced in a USDA-licensed establishment shall be produced under a U.S. Veterinary Biological Product License or a license granted by a State under § 107.2 (referred to as a State biological product license and the products prepared pursuant thereto as State-licensed biological products, including autogenous biologics), but not under both a U.S. Veterinary Biological Product License and a State biological product license. Before a U.S. Veterinary Biological Product License (including a conditional license) is issued, the licensee shall relinquish its State license for that product: *Provided*, That autogenous biologics shall not be subject to this provision when they are prepared in accordance with the provisions of paragraph (c)(5) of this section.

(1) State-licensed biological products (including autogenous biologics) shall only be distributed or shipped intrastate, must not bear a U.S. Veterinary

Biologics Establishment License Number, and must not otherwise be represented in any manner as having met the requirements for a U.S. Veterinary Biological Product license. Labeling of State- and USDA-licensed biological products produced in the same establishment must be distinctly different in color and design.

(2) All biological products in USDA-licensed establishments, whether licensed by USDA or by the State, shall be prepared only in locations indicated in legends filed in accordance with 9 CFR part 108. A description of each State-licensed product must be filed with the Animal and Plant Health Inspection Service as part of the blueprint legends and must be sufficient for Animal and Plant Health Inspection Service to determine any risk to the production of other products in the licensed establishment and to determine that adequate procedures are followed to prevent contamination during production.

(3) Records in such establishments must be maintained in accordance with §§ 116.1 and 116.2 of this subchapter and shall include all products licensed by the State or USDA.

(4) Reports prescribed in § 116.5 of this subchapter for USDA-licensed establishments shall be submitted for all veterinary biological products in the establishment.

(5) Under the following conditions, an autogenous biologic may be produced in a USDA-licensed establishment under either a State or U.S. Veterinary Biological Product License:

(i) When a culture of microorganisms, isolated from a herd in a State, is received at a USDA-licensed establishment that is in the same State but that holds both a State and a U.S. Veterinary Biological Products License for autogenous biologics, the isolate shall be designated by the licensee for use in the production of an autogenous biological product under either the State product license, or the U.S. Veterinary Biological Product License: *Provided*, That the isolate meets the requirements of the respective regulatory authority for an autogenous biologic. If, after producing the product pursuant to one license, the licensee elects to produce an autogenous biologic from